Original article

Entecavir versus lamivudine in the treatment of chronic hepatitis B patients with hepatic decompensation

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Background: Lamivudine has been widely used in chronic hepatitis B patients with hepatic decompensation, but its use is limited by drug resistance. This outcome research aimed to investigate the comparative efficacy and safety of entecavir versus lamivudine in decompensated patients.
Methods: Between November 2004 and February 2010, 126 consecutive treatment-naive patients received either entecavir (*n*=53) or lamivudine (*n*=73) for decompensated chronic hepatitis B. All patients presented with both hyperbilirubinaemia and coagulopathy. Primary outcome was mortality within 1 year; secondary outcomes included liver-related mortality, biochemical and virological response, and improvement of hepatic dysfunction.
Results: Both treatment groups were comparable in baseline characteristics. A total of 19 (35.8%) entecavir and 33 (45.2%) lamivudine receivers expired within 1 year, respectively (*P*=0.29, log rank test). Age (hazard ratio [HR] 1.04 per year, 95% CI 1.01, 1.06), cirrhosis (HR 2.07, 95% CI 1.02, 4.23), and international normalized ratio for prothrombin time (HR 1.44, 95% CI 1.20, 1.74) were independent baseline predictors for all-cause mortality. Antiviral therapy was also unrelated to liver-specific death. However, more patients taking entecavir tended to attain aminotransferase normalization (76.5% versus 52.5%; *P*=0.05) and viral DNA undetectability (100% versus 58.3%; *P*=0.06). Moreover, entecavir was associated with significantly greater reduction of the model for end-stage liver disease scores (median 10.0 versus 4.3; *P*=0.02). Overall, 3 (7.5%) lamivudine but no entecavir users acquired drug resistance in 1 year (*P*=0.25).
Conclusions: Entecavir as compared with lamivudine is similar in the effect on short-term mortality but is associated with greater clinical improvement among chronic hepatitis survivors who recovered from hepatic decompensation.

Introduction

Chronic infection with HBV is a global disease, affecting approximately 350 million people worldwide [1]. The morbidity and mortality associated with chronic hepatitis B (CHB) are substantial in that 15% to approximately 40% of infected patients will develop serious sequels including persistent hepatitis, hepatic failure, liver cirrhosis and hepatocellular carcinoma (HCC) during their lifetime [2,3]. Hepatic failure is a leading cause of death in CHB patients and may result from progressive functional loss of cirrhotic livers and extensive hepatic necrosis following episodes of severe acute exacerbation (SAE) [4–6]. Prompt recognition and early institution of multidisciplinary management are mandatory in decompensated patients, but short-term mortality remains high with standard supportive care [7–11].

Oral nucleoside/nucleotide analogues (NUCs) are direct inhibitors of HBV polymerase that potently suppress viral replication and effectively reduce hepatic necroinflammation. By contrast with interferon, which may aggravate hepatitis and therefore is contraindicated in those with decompensated liver diseases, NUC is the only antiviral therapy recommended for CHB patients with hepatic failure [12–14]. Being the first NUC approved for the treatment of CHB, lamivudine has been widely used in decompensated patients, and may effectively improve liver function, stabilize disease progression, and even obviate indications for transplantation [8,9,15–17]. However, lamivudine is becoming less favoured as a first-line antiviral agent because of its lower genetic barrier to the development

of drug resistance [18]. More potent NUCs with lesser risk of resistance are generally preferred over lamivudine [13,14], but comparative research regarding these newer agents in the treatment of decompensated patients remains strikingly sparse.

Entecavir is a newer NUC with significantly stronger antiviral efficacy as compared with lamivudine [19–21]. The cumulative resistance rate to entecavir after 5 years of therapy was reported to be as low as 1.2% in NUC-naive patients [22]. It appears that, at least theoretically, entecavir may substitute lamivudine in patients with hepatic decompensation. Nevertheless, clinical data are inconsistent with regard to the efficacy and safety of entecavir in this clinical setting [23–27]. Of particular note, it has been reported that entecavir was related to potentially fatal lactate acidosis in severely decompensated cirrhotic patients [23], and was associated with increased risk of 48-week mortality in icteric CHB patients with SAE [25].

In order to elucidate whether entecavir was effective and safe in CHB patients with hepatic decompensation, this study aimed to compare clinical outcomes of decompensated patients treated with entecavir versus those with lamivudine.

Methods

Study setting and population

This retrospective comparative research was conducted in a regional teaching hospital (E-Da Hospital, Kaohsiung) in southern Taiwan, and was approved by the local institutional review board. All adult (age >20 years) patients with CHB infection who received NUCs from November 2004 to February 2010 were screened for eligibility. Patients were enrolled if they fulfilled all of the inclusion criteria that comprised serum hepatitis B surface antigen (HBsAg) positivity for >6 months, hepatic decompensation defined as presence of both hyperbilirubinaemia (raised serum bilirubin level higher than 2× the upper limit of normal) and coagulopathy (prolonged prothrombin time greater than three seconds) [12], and antiviral therapy with either entecavir or lamivudine for a minimum of 1 week duration. The exclusion criteria were suspected or confirmed liver diseases from aetiologies other than HBV (such as alcohol, toxin, drug, shock and acute viral hepatitis A or E), coinfection with HIV, HCV or HDV, and prior antiviral treatment with NUCs. The diagnosis of cirrhosis was based principally on clinical and sonographic assessment. In patients whose sonographic diagnoses were indeterminate, those with unequivocal oesophageal or gastric varices were considered as having cirrhosis because sonography was less sensitive for liver cirrhosis caused by CHB [28]. An episode of SAE was defined as elevated serum alanine aminotransferase (ALT)>10×the upper limit of normal and >2× the baseline value [14,29]. Presence of cirrhosis and SAE were not mutually exclusive by definition. Development of ascites and/or encephalopathy within 4 weeks of severe hepatitis flares defined acute on chronic liver failure (AOCLF) [30].

Antiviral therapy and laboratory measurement

All eligible patients managed in this hospital prior to August 2008 received lamivudine since entecavir was not reimbursed in Taiwan until then. Afterward, the vast majority of enrolled patients received entecavir. The daily dosage of lamivudine was 100 mg and that of entecavir was 0.5 mg in most cases but might occasionally vary according to individual patient's condition (for example, renal insufficiency). Whichever medication was taken, it was continued throughout the 1-year study period unless death, drug resistance or loss to follow-up occurred. Since this study was not prospectively designed, patients were followed up at the discretion of treating physicians without a strict protocol. Generally, serum aminotransferases and other biochemical indicators of liver function were assayed 1–3× per week during hospitalization and on a monthly basis at outpatient care. Viral serology (HBsAg, antibody against HBsAg, hepatitis B e antigen [HBeAg] and antibody against HBeAg) was determined every 6–12 months by commercially available immunoassays (ABBOTT GmbH & Co., Wiesbaden, Germany). Serum HBV DNA was measured with time interval of 6–12 months or on suspicion of drug resistance by the quantitative method of branched DNA assay (VERSANT 440 Molecular System, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). The detection range of HBV DNA was 2,000–100,000,000 copies/ml, which was logarithmic transformed (3.3–8 log copies/ml) for presentation in this study. HBV DNA<2,000 copies/ml was taken as 1 copy/ml (0 log copy/ml) and >100,000,000 copies/ml as 1,000,000,000 copies/ml (9 log copies/ml) for calculation. Genetic analysis for resistant mutations was performed in all patients with confirmed virological breakthrough defined as 10-fold increase in serum HBV DNA above nadir.

Definitions of study outcomes

Primary outcome was death from all causes within 1 year. Secondary outcomes included liver-related mortality, normalization of serum ALT, undetectability of HBV DNA, HBeAg seroconversion in HBeAg-positive patients, change of model for end-stage liver disease (MELD) scores [31], and emergence of drug resistance, which required virological breakthrough and subsequent confirmation of genetic resistance. All secondary outcomes were determined at the time point of 1 year after NUC therapy.

Table 1. Baseline characteristics of chronic hepatitis B patients with hepatic decompensation stratified by antiviral treatment with lamivudine or entecavir

Characteristics	All patients (*n*=126)	Lamivudine (*n*=73)	Entecavir (*n*=53)	*P*-value[a]
Age, years	47 (37–57)	46 (37–58)	48 (40–56)	0.48
Male gender	98 (77.8)	58 (79.5)	40 (75.5)	0.67
HBeAg-positive	35 (27.8)	17 (23.3)	18 (34.0)	0.23
HBV DNA, log copies/ml	6.82 (5.09–9.00)	6.78 (4.40–9.00)	7.02 (5.72–8.74)	0.47
AST, IU/l	407 (139–1,132)	445 (138–1,233)	395 (140–1,103)	0.66
ALT, IU/l	452 (76–1,175)	467 (68–1,530)	391 (78–879)	0.56
Bilirubin, mg/dl	8.3 (3.5–14.3)	8.9 (4.3–15.3)	7.5 (3.3–13.4)	0.29
INR	1.59 (1.41–1.96)	1.66 (1.43–2.08)	1.52 (1.39–1.85)	0.09
Creatinine level, mg/dl	1.1 (0.9–1.2)	1 (0.9–1.3)	1.1 (0.9–1.2)	0.81
Platelet count, 10^3 cells/μl	112 (64–148)	112 (70.5–117)	112 (53–139)	0.49
Haemoglobin, g/dl	12.6 (10.1–14.5)	12.6 (9.8–14.7)	12.1 (10.6–14.3)	0.92
Leukocyte count, cells/μl	6,520 (4,680–8,900)	6,765 (4,865–9,150)	6,080 (4,090–8,490)	0.17
Acute exacerbation	64 (50.8)	38 (52.1)	26 (49.1)	0.86
AOCLF	31 (24.6)	21 (28.8)	10 (18.9)	0.22
Cirrhosis	59 (46.8)	35 (48.0)	24 (45.3)	0.86
Ascites	46 (36.5)	26 (35.6)	20 (37.7)	0.85
MELD score	19.6 (16.0–25.1)	20.4 (16.5–26.5)	18.6 (15.8–23.8)	0.23

Data are expressed as median (IQR) or *n* (%). [a]*P*-values for comparisons between lamivudine and entecavir receivers. ALT, alanine aminotransferase; AOCLF, acute on chronic liver failure; AST aspartate aminotransferase; HBeAg, hepatitis B e antigen; INR, international normalized ratio; MELD, model for end-stage liver disease.

Data analysis

All statistical analysis was performed by commercial software package (Stata version 9.0; Stata Corporation, College Station, TX, USA). Continuous variables were expressed with median and IQR, and were compared between groups by the Mann–Whitney U test. Categorical variables were expressed with proportion, and Fisher's exact test was applied for comparison. Kaplan–Meier survival curves of the two treatment groups were plotted and compared by the log-rank test to examine difference in survival. Risk factors associated with survival were identified by the Cox proportional hazard model, and the result was reported as hazard ratio (HR) with 95% CI. All statistical tests were two-sided with significance set at *P*-value <0.05.

Results

Baseline characteristics of CHB patients with hepatic decompensation

A total of 167 CHB patients presenting with hepatic decompensation were treated with either lamivudine or entecavir during the study period, and 41 ineligible patients were excluded because of HCC in 28, coinfection with HCV in 9 and prior exposure to NUC in 4 patients. Among the 126 patients enrolled into analysis. Seventy-three and 53 received lamivudine and entecavir, respectively. Baseline characteristics did not significantly differ between the two treatment groups upon initiation of antiviral therapy (Table 1). Among the 64 patients with SAE, 31 fulfilled the definition of AOCLF with 21 and 10 patients receiving lamivudine and entecavir respectively (*P*=0.22). A total of 12 (18.8%) of the patients with SAE had identifiable triggering factors with 5 (7.81%) receiving cytotoxic chemotherapy, 4 (6.26%) taking steroid or immunosuppressant for autoimmune disorders, 2 (3.13%) having severe sepsis and 1 (1.56%) suffering from bleeding-related hypovolemic shock. However, most patients (*n*=52, 81.3%) with preceding episodes of marked serum ALT elevation could only be ascribed to spontaneous viral reactivation.

All-cause and liver-related mortality within 1 year

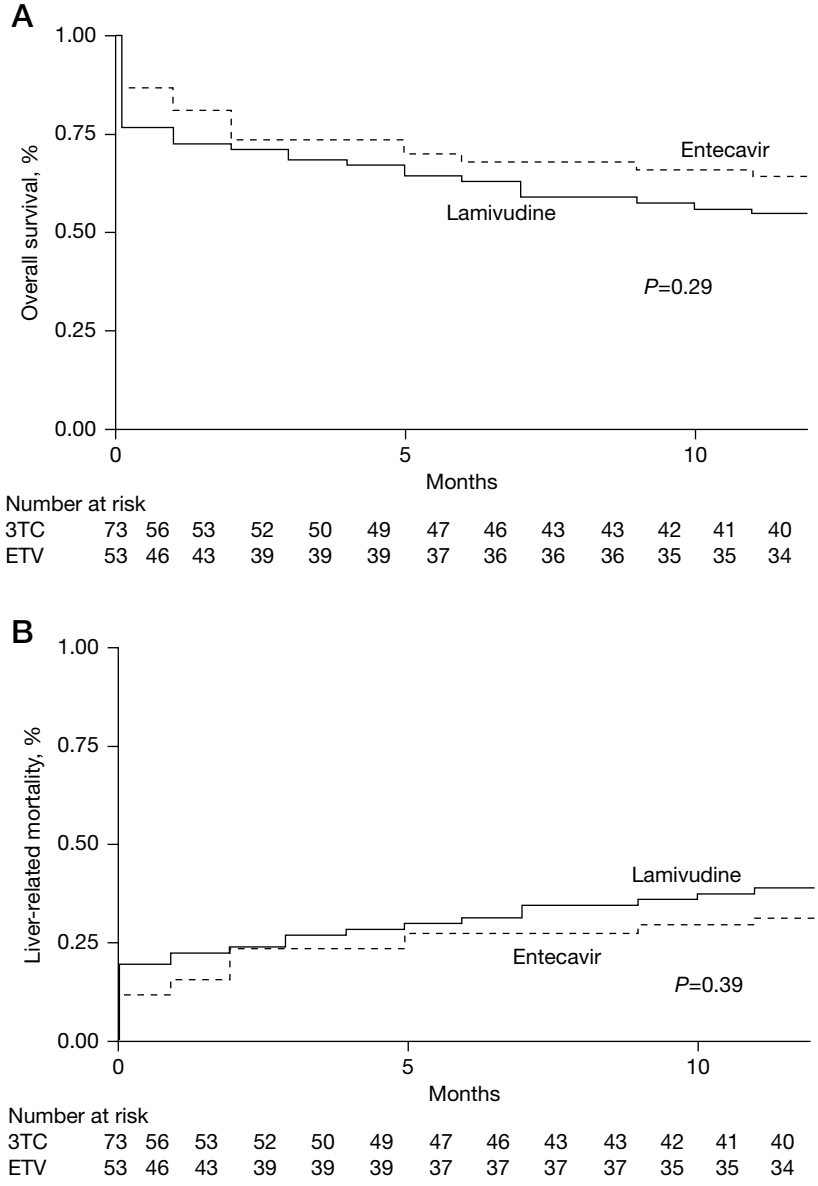
Overall, 52 patients died within 1 year, with most of them (*n*=42, 80.8%) succumbing within the first 6 months. Approximately one-half of the deaths (*n*=24, 46.2%) occurred in the first month (Additional file 1). Among these mortality cases, 33 (out of 73, 45.2%) and 19 (out of 53, 35.8%) were in the lamivudine and entecavir group, respectively. The survival curves were not statistically different between the two treatment groups (Figure 1A). This result was consistent in patients with underlying cirrhosis as well as in those with SAE (Additional file 2). A total of 43 (82.3%) out of the 52 deaths were related to progressive liver failure, whereas 9 patients died from the following causes: terminal malignant diseases other than HCC (*n*=3), intracranial haemorrhage (*n*=2), sepsis (*n*=2), aneurysmal rupture (*n*=1) and fatal arrhythmia (*n*=1). Similar to all-cause mortality, most (*n*=35, 81.4%) of the liver-related deaths occurred in the first 6 months with nearly one-half (*n*=20, 46.5%) of them within the first month. The liver-related mortality rates were not different between the two treatment groups (Figure 1B).

None of the enrolled patients underwent liver transplantation during the study period.

Baseline predictors associated with all-cause and liver-related mortality

Univariate analysis revealed pretreatment characteristics including age, serum bilirubin, international normalized ratio (INR), haemoglobin level, AOCLF, cirrhosis and MELD score were associated with 1-year survival (Table 2). Independent risk factors for mortality were age (HR 1.04 per year, 95% CI 1.01, 1.06), INR (HR 1.44 per unit, 95% CI 1.20, 1.74) and presence of cirrhosis (HR 2.07, 95% CI 1.02, 4.23). With regard to the liver-related mortality, univariate predictive factors were serum bilirubin, INR, AOCLF, cirrhosis and MELD score (Additional file 3). Independent pretreatment predictors for liver-related death included serum level of HBV DNA (HR 1.23 per log IU/ml, 95% CI

Figure 1. Kaplan–Meier estimates of cumulative overall survival and liver-related mortality



(A) Cumulative overall survival and **(B)** liver-related mortality in patients with decompensated liver disease due to chronic hepatitis B, according to antiviral treatment with lamivudine (3TC) or entecavir (ETV).

1.03, 1.46), INR (HR 1.69 per unit, 95% CI 1.33, 2.12) and cirrhosis (HR 3.53, 95% CI 1.46, 8.55).

Biochemical, virological and serological outcomes after 1 year of antiviral therapy

Entecavir tended to outperform lamivudine among patients who survived for >1 year (n=74) in terms of biochemical and virological responses, because antiviral therapy with entecavir as compared with lamivudine resulted in more patients with ALT normalization (76.5% versus 52.5%; P=0.05) and HBV DNA undetectability (100% versus 58.3%; P=0.06; Figure 2A). The 1-year rates of HBeAg seroconversion were not different between the two treatment groups (Figure 2B). Three patients acquired drug resistance to lamivudine within 1 year, in all of whom biochemical and virological breakthrough was noted first, and emergence of YMDD mutants was confirmed by genetic analysis later. They were managed with add-on adefovir (10 mg per day). Pretreatment serum HBV DNA was 7.47 log IU/ml in one and >9 log IU/ml in the other two patients. No resistance to entecavir was detected (P=0.25).

Parameters regarding hepatic reserve, including INR for prothrombin time, serum bilirubin level and MELD score, all improved after 1 year of antiviral therapy in both treatment groups (Table 3). Improvement of these indicators was numerically greater in the entecavir receivers, although difference in the decrease of serum bilirubin was statistically insignificant. Of note, the median reduction of MELD score was 10.0 (95% CI 6.8, 11.9) in the entecavir group, which was significantly higher than 4.3 (95% CI 2.4, 5.3) in the lamivudine group (P=0.02). No patients, whether on entecavir or lamivudine, discontinued medication because of side effects ascribed to the NUC.

Discussion

This outcome research explored the comparative efficacy and safety of entecavir versus lamivudine for CHB patients with hepatic decompensation. Neither overall mortality nor liver-specific mortality were associated with the choice of antiviral therapy. The 1-year fatality rate was independently associated with age, cirrhosis, and INR, but unrelated to which NUC was taken. Although entecavir and lamivudine were not different in the effect on short-term mortality, entecavir tended to be associated with superior efficacy in ALT normalization and HBV DNA undetectability. Moreover, improvement of hepatic dysfunction as indicated by reduction of MELD score was significantly more pronounced in the entecavir receivers (P=0.02) than their lamivudine counterparts.

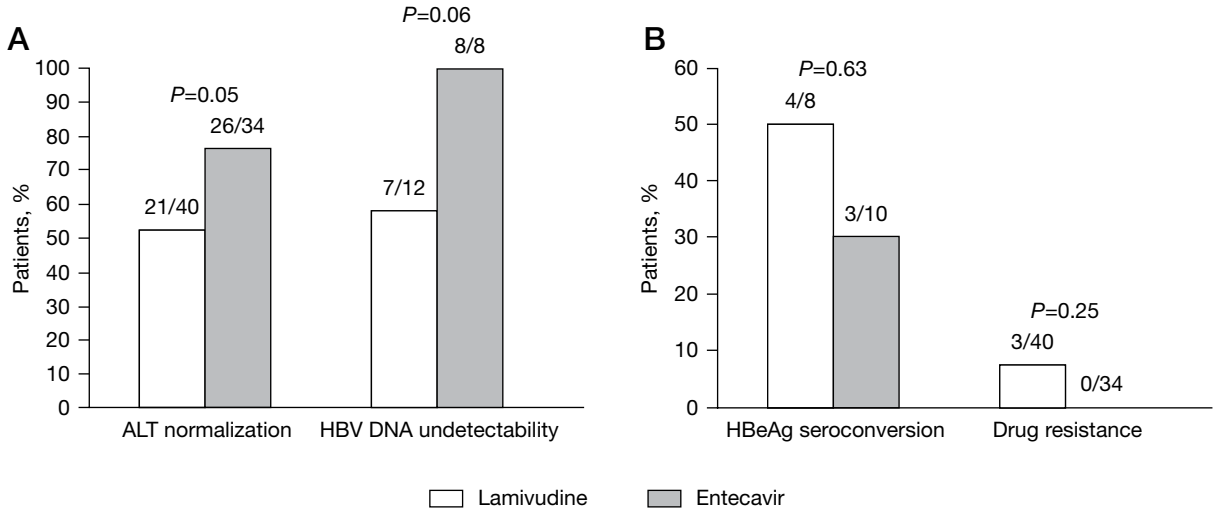
Previous studies have demonstrated that baseline serum HBV DNA was predictive of poor prognosis in CHB patients with hepatic decompensation resulting from cirrhosis as well as from SAE [8,32]. This association rationalized the institution of viral suppression in decompensated liver diseases due to CHB. Garg *et al*. [11] have demonstrated in a randomized

Table 2. Predictive factors associated with 1-year mortality by univariate and multivariate analysis

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
Age per year older	1.02	1.00, 1.04	0.022	1.04	1.01, 1.06	0.006
Male gender	1.07	0.55, 2.08	0.847	–	–	–
Entecavir use[a]	0.75	0.43, 1.32	0.316	–	–	–
HBeAg-positive	0.75	0.39, 1.43	0.388	–	–	–
HBV DNA per log copies/ml	1.00	0.87, 1.14	0.998	–	–	–
AST per IU/l	1.00	1.00, 1.00	0.910	–	–	–
ALT per IU/l	1.00	1.00, 1.00	0.347	–	–	–
Bilirubin per mg/dl	1.04	1.01, 1.08	0.004	–	–	–
INR per unit	1.50	1.29, 1.76	<0.001	1.44	1.20, 1.74	<0.001
Creatinine per mg/dl	1.07	0.95, 1.20	0.279	–	–	–
Platelet count per 10^3/cells/μl	1.00	0.99, 1.00	0.471	–	–	–
Haemoglobin per g/dl	0.86	0.77, 0.96	0.005	–	–	–
Leukocyte count per cells/μl	1.00	0.97, 1.04	0.739	–	–	–
Acute exacerbation	0.85	0.49, 1.46	0.556	–	–	–
AOCLF	2.27	1.28, 4.00	0.005	–	–	–
Cirrhosis	1.77	1.02, 3.08	0.044	2.07	1.02, 4.23	0.045
Ascites	1.50	0.87, 2.59	0.147	–	–	–
MELD score	1.07	1.04, 1.09	<0.001	–	–	–

[a]As compared with the use of lamivudine. ALT, alanine aminotransferase; AOCLF, acute on chronic liver failure; AST aspartate aminotransferase; HBeAg, hepatitis B e antigen; HR, hazard ratio; INR, international normalized ratio; MELD, model for end-stage liver disease.

Figure 2. Biochemical, virological and serological responses and drug resistance 1 year after treatment



(A) Biochemical and virological responses. Entecavir tended to be associated with more patients achieving normalization of serum alanine aminotransferase (ALT) and undetectability of HBV DNA. **(B)** Hepatitis B e antigen (HBeAg) and drug resistance. Rates of HBeAg seroconversion and emergence of drug resistance were similar between the two treatment groups.

Table 3. Change of parameters indicative of hepatic function after 1 year of antiviral therapy

Parameter	Overall (*n*=74)	Lamivudine (*n*=40)	Entecavir (*n*=34)	*P*-value[a]
Decrease in bilirubin, mg/dl	4.0 (1.4–9.3)	3.5 (1.4–7.1)	7.7 (1.4–12.1)	0.22
Decrease in INR	0.26 (0.19–0.44)	0.22 (0.07–0.27)	0.38 (0.26–0.48)	0.05
Decrease in MELD scores	5.6 (2.4–10.0)	4.3 (2.4–5.3)	10.0 (6.8–11.9)	0.02

Data are expressed as median (IQR). [a]*P*-values for comparisons between lamivudine and entecavir receivers. INR, international normalized ratio; MELD, model for end-stage liver disease.

placebo-controlled trial that rapid HBV reduction (≥2 log decrease by day 15) achieved by tenofovir accurately predicted survival in patients with CHB-related AOCLF, providing direct evidence for inhibiting HBV replication among decompensated patients. It follows reasonably that a more potent inhibitor of HBV DNA polymerase should confer clinical advantages over a weaker one in decompensated CHB, but data from comparative studies evaluating different NUCs remains inconclusive to date [25–27,33]. Similar to our findings, a multicentre randomized trial recently reported that entecavir was superior to adefovir in antiviral potency, biochemical remission and clinical improvement (measured in Child-Turcotte-Pugh along with MELD scores) in CHB patients with evidence of hepatic decompensation, although mortality rates and HCC incidences were not different between the treatment groups [27]. How to explain the discrepancy between laboratory improvement and survival benefits is unclear, but insufficient sample size and inadequate observation period are probable explanations. Taking our research for example, we estimated *post hoc* a minimum of 916 subjects (458 per treatment group) would be needed to statistically distinguish the differences in 1-year mortality rates (35.8% versus 45.2%), with α-level of 0.05 and power set at 0.80, should the null hypothesis be false. Besides, hepatic decompensation in some patients may already reach irreversibility beyond rescue of viral suppression [8,25], and hence antiviral therapy would not influence the short-term mortality. Further research with large number of patients, long periods of observation or meta-analyses of similar studies are warranted to elucidate the uncertainty.

There has been a particular concern for administering entecavir in severely decompensated liver diseases since a case series linked entecavir with fatal lactate acidosis in patients with pretreatment MELD score >20 points [23]. However, in clinical trials for patients with decompensated liver disease due to CHB, lactate acidosis rarely occurred in entecavir receivers and did

not affect the safety profile as compared with other NUCs [26,27]. The retrospective design of our study precluded the possibility of determining if entecavir or lamivudine receivers were prone to develop lactate acidosis, but the severity of hepatic dysfunction of participants (median MELD score of 19.6, IQR 16.0–25.1) offered an opportunity to examine whether entecavir would be detrimental among severely decompensated patients. Based on our data, there was no reason to believe entecavir as compared with lamivudine was associated with any serious side effect that had influenced clinical outcomes. Interestingly, a non-randomized comparative study conducted by Wong *et al.* [25] showed that entecavir as opposed to lamivudine was independently associated with 48-week mortality in CHB patients with SAE (HR 5.1, 95% CI 1.5, 17.2; P=0.01), despite a more rapid virological suppression and higher rates of virological and biochemical response at week 48. What caused the association of entecavir with excessive mortality in the study by Wong *et al.* [25] was not completely understood, but as the authors pointed out in the article, age might at least in part confound the results because their entecavir recipients were significantly older (mean ±SD 51 ±13 versus 44 ±14 years; P=0.005). Randomized controlled trials comparing entecavir against lamivudine in decompensated patients is preferred to resolve the controversy, but are understandably difficult to conduct.

Strengths of this study include strict laboratory criteria to screen consecutive patients for eligibility. Reimbursement for NUCs by Taiwan National Health Insurance requires documentation of pertinent biochemical, serological and virological data before therapy, which helps reduce bias in patient selection. In addition, study end points along with analysed parameters are all objective measurements, avoiding the variability related to subjective judgment. Moreover, the matched baseline characteristics support comparability between the two treatment groups. Finally, mortality rates are consistent in the overall and subgroup analyses, and are reaffirmed by multivariate regression modelling. Similarly the superiority of entecavir over lamivudine in clinical improvement among survivors is consistent from different angles of evaluations.

Apart from the aforementioned possibility of type II error, several limitations of this study merit attention and discussion. First, since the treatment assignment was primarily based on when the patient was managed, it may be argued that patient care improved with time and such allocation bias would favour the more recent entecavir-treated cohort. Nonetheless, with a study period shorter than 6 years, it is unlikely that the supportive care has improved so much to have seriously affected clinical outcomes. Second, there is no standardized protocol for monitoring on-treatment serum HBV DNA because routine testing for HBV DNA during NUC therapy is regrettably not reimbursed in Taiwan. Actually, HBV DNA after 1 year of therapy was checked in some but not all participants. Although we believe these measured samples are representative, we acknowledge that lack of regular surveillance for serum HBV DNA may delay detection of genetic resistance and lead to underestimation of resistance rate. Nevertheless, the apparently low resistance rate to lamivudine (3/40, or 7.5%) may also result from the characteristics of this patient group, half of whom present with SAE. It has been shown that the risk of lamivudine resistance was lower in patients with SAE than in those with usual HBeAg-positive or HBeAg-negative CHB [34,35]. Third, cirrhosis may have been underdiagnosed because diagnosis is mainly based on sonographic criteria, which are relatively insensitive for CHB-induced cirrhosis [28]. Finally, drug compliance and immediate cause of death cannot be ascertained, as would be expected for a retrospective study.

In conclusion, entecavir does not differ from lamivudine in short-term mortality in CHB patients with decompensated liver diseases, but it appears more efficacious in improving hepatic dysfunction among those who survived for >1 year. These findings support the efficacy and safety of entecavir as one of the first-line antiviral therapies for patients with decompensated liver diseases due to CHB.

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Disclosure statement

The authors declare no competing interests.

Additional files

Additional file 1: A table displaying mortality rates between decompensated patients treated with lamivudine and those with entecavir can be accessed via http://www.intmedpress.com/uploads/documents/AVT-11-OA-2212_Hsu_Add_file1.pdf

Additional file 2: A figure illustrating survival curves for the lamivudine and entecavir groups,

stratified by SAE and cirrhosis, can be accessed via http://www.intmedpress.com/uploads/documents/AVT-11-OA-2212_Hsu_Add_file2.pdf

Additional file 3: A table displaying predictive factors associated with liver-related mortality within 1 year by univariate and multivariate analysis can be accessed via http://www.intmedpress.com/uploads/documents/AVT-11-OA-2212_Hsu_Add_file3.pdf

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